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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,188	06/02/2005	Niall Gormley	2713-1-015PCT/US	1232

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,188	GORMLEY ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 27-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 27-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/17/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 20, 2008 has been entered.

Claims 4 and 27-33 are currently pending. Claims 4 and 27-28 have been amended. Claim 33 is newly presented.

Withdrawn Objections

2. The objection made to claim 28 in the Office Action of July 18, 2008 is withdrawn in view of the amendment made to the claim.

Withdrawn Rejections

3. The rejections made under 35 USC 112 2nd paragraph in section 5 of the Office Action of July 18, 2008 are withdrawn in view of amendments made to the claims.

The rejections made under 35 USC 103(a) in sections 7-8 of the Office Action of July 18, 2008 are withdrawn in view of Applicants arguments and amendments made to the claims.

Claim Objections

4. Claim 4 is objected to because the preamble recites "a method for sequencing nucleic acid", however the method results in sequencing several different nucleic acids, rather than a single nucleic acid. This objection can be overcome by amending the preamble to recite "a method for sequencing nucleic acids". Also step (c) should be modified to recite "removing the complementary copy of the template sequences".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30 and 32-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 recites the limitation "the 10^6-10^9 templates". There is insufficient antecedent basis for this limitation in the claim because although the claims previously refer to "10^6-10^9 different template sequences" they do not refer to a "10^6-10^9 templates".

Claim 32 recites the limitation "the fluorescent nucleotides". There is insufficient antecedent basis for this limitation in the claims because although the claim previously refer to "fluorescently labeled nucleotides" they do not refer to "fluorescent nucleotides".

Claim 33 recites the limitation "a complementary strand on the template strand". There is insufficient antecedent basis for this limitation. This rejection may be overcome by modifying the claims to recite i.e., "a complementary sequence one base at a time".

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a new ground of rejection:

7. Claims 4, 27-28, 30-31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanisn (WO 01/57248 Pub 9/2001) as evidenced by

Cheeseman (US Patent 5302509 Issued 1994), in view of Soper (US Patent 5846727) and Parker (US Patent 5565323).

Regarding Claim 4 Balasubramanisn teaches a method comprising forming an array of polynucleotide molecules immobilized on a solid surface. Each polynucleotide has a hairpin loop structure wherein one end of hairpin loop structure acts as a primer and the other end of the hairpin loop structure acts as a template (page 3, lines 11-14 and page 4 line 28 to page 5 line 7). Balasubramanisn further teaches that the polynucleotides are attached to the array at a density of between 10^6-10^9 sequences per cm^2. Balasubramanisn also teaches determining the sequence of the template nucleic acid by synthesizing a complementary nucleic acid strand. Specifically Balasubramanisn cites the method of Cheeseman as a suitable sequencing method (page 7, lines 24-31). The method of Cheeseman comprises contacting the template with fluorescently labeled 3' blocked nucleotide triphosphates, with each of the bases having a different fluorescent label and a polymerase. The DNA polymerase causes selective addition of only the complementary labeled NTP, thus identifying the next unpaired base in the unknown strand. The 3' blocking group is then removed, setting the system up for the next NTP addition and so on (Abstract). Regarding Claims 27 and 28 Balasubramanisn teaches a method wherein the template polynucleotides are attached to a double stranded anchor wherein the double stranded anchor is a complementary hairpin (page 4 line 28 to page 5 line 7). Regarding Claim 30 Balasubramanisn teaches that the templates are individually resolvable (page 4, line 11). Regarding Claim 31 Balasubramanisn teaches a method wherein the sequencing

determination is carried out using cycles of incorporation and detection of fluorescently labeled nucleotides. Specifically Balasubramanisn refers to the method of Cheeseman which teaches this (see Cheeseman abstract). Regarding Claim 33 Balasubramanisn teaches a method which employs a polymerase enzyme to synthesize a complementary strand one base at a time. Specifically Balasubramanisn cites the method of Cheeseman which teaches using Taq polymerase (see Cheeseman Col 3, line 67).

Balasubramanisn does not teach a method further comprising removing the complementary copy of the template sequence and performing a second round of sequencing (clm 4).

However Soper teaches a sequencing method wherein after primer extension the extension products are removed from the immobilized templates by denaturing with mild aqueous alkali. Soper then teaches that after the extension products have been removed the biotinylated template is ready for "resequencing" if desired (Col 8, lines 54-61). Thus Soper teaches a method further comprising removing the complementary copy of the template sequence and performing a second round of sequencing.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanisn by removing the complementary strand and resequencing the template as suggested by Soper. The rationale to support a conclusion that the claims would have been obvious is that all of the claimed method steps were known in the prior art and one skilled in the art could have arrived at the claimed invention by combining the steps that were taught

in the prior art. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore the invention as a whole was prima facie obvious to one or ordinary skill in the art at the time the invention was made, as evidenced by the references.

The combined teachings of Balasubramanisn and Soper do not teach comparing the first and second rounds of sequencing to confirm sequencing data.

However Parker teaches a method wherein multiple sequences are obtained and then the sequences are aligned and compared with published sequences. Mutations were noted and then confirmed by resequencing the variant regions (col 15, lines 50-54). Thus Parker teaches comparing multiple sequences to confirm sequencing data.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanisn and Soper by comparing the first and second rounds of sequencing to confirm sequencing data as suggested by Parker. It would have been obvious to one of skill in the art to compare the obtained sequences in order to confirm that the obtained sequences were identical. The rationale to support a conclusion that the claims would have been obvious is that all of the claimed method steps were known in the prior art and one skilled in the art could have arrived at the claimed invention by combining the steps that were taught in the prior art. Further one of skill in the art would have had a reasonable expectation of success in doing so.

The following is a new ground of rejection:

8. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanisn (WO 01/57248 Pub 9/2001) as evidenced by Cheeseman (US Patent 5302509 Issued 1994) in view of Soper (US Patent 5846727) and Parker (US Patent 5565323) as applied to claims 4 and 27 above and in further view of Lackey (US Patent 5652126).

The teachings of Balasubramanisn (evidenced by Cheeseman), Soper, and Parker are presented above.

The combined references do not teach a method wherein the double stranded anchor (which acts as a primer) comprises a recognition site for a restriction endonuclease.

However Lackey teaches a method that comprises synthesizing a complementary copy nucleic acid sequence using a template sequence. Lackey further teaches when a DNA primer/template with a single 3' ribonucleotide is used, cleavage at the ribonucleotide residue, followed by separation and purification of the oligonucleotide product, results in a fully regenerated and reusable primer/template (Col 13, lines 26-31). Lackey further teaches that cleavage may be performed using a site specific restriction endonuclease, alkaline hydrolysis or an endonuclease such as RNase (col 12, lines 42-47). Thus Lackey teaches a method wherein the primer has a recognition site for a restriction endonuclease.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanisn, Soper, and Parker by using a double stranded anchor (that acts as a primer) that comprises a recognition site for a restriction endonuclease. The use of such a double stranded anchor would be beneficial because primer extension products could easily be removed by using a restriction endonuclease that cuts at the recognition site thereby allowing the template and the primer to be reused. Since all of the claimed method steps were known in the art, one of skill could have combined these methods and the combination would have yielded predictable results.

The following is a new ground of rejection:

9. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanisn (WO 01/57248 Pub 9/2001) as evidenced by Cheeseman (US Patent 5302509 Issued 1994) in view of Soper (US Patent 5846727) and Parker (US Patent 5565323) as applied to claims 4 and 31 above and in further view of Barnes (WO 01/57249 Pub 8/2001).

The teachings of Balasubramanisn (evidenced by Cheeseman), Soper, and Parker are presented above.

The combined references do not teach a method wherein the fluorescent nucleotides are detected using a microscope with total internal reflection based imaging.

However Barnes teaches that using total internal reflection fluorescent microscopy it is possible to achieve wide field imaging with single polymer sensitivity.

This allows arrays of greater than 10^7 resolvable polymers per cm^2 to be used (page 6, lines 9-14).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Balasubramanisn, Soper, and Parker by using a microscope with total internal reflection to detect the incorporation of each nucleotide as suggested by Barnes particularly since Barnes teaches it is possible to achieve wide field imaging with single polymer sensitivity and that this allows arrays of greater than 10^7 resolvable polymers per cm^2 to be used. Therefore it would have been obvious to use the detection method disclosed by Barnes for the benefit of being able to detect a large number of individual fluorescent nucleotides present on the array.

Conclusion

10. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Carla Myers/
Primary Examiner, Art Unit 1634